4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 300, 330, and 610

[Docket No. FDA-2015-N-1260]

Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to revise its regulations on prescription fixed-combination drugs to apply the regulations to both prescription and nonprescription fixed-combination and co-packaged drugs and combinations of active ingredients under consideration for inclusion in an over-the-counter (OTC) monograph. These products must meet specific evidentiary requirements for approval. The proposed revisions would harmonize the requirements for prescription and nonprescription products and make them consistent with long-standing Agency policy.

DATES: Submit either electronic or written comments on this proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 (the PRA) by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER] (see the "Paperwork Reduction Act of 1995" section of this document). See section IX of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments by any of the following methods, except that comments on information collection issues under the PRA must be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) (see the "Paperwork Reduction act of 1995" section of this document):

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Docket No. FDA-2015-N-1260 for this rulemaking. All comments received may be posted without change to http://www.regulations.gov, including any personal information provided. For additional information on submitting comments, see the "Request for Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to http://www.regulations.gov and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Diana Pomeranz, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6208, Silver Spring, MD 20993, diana.pomeranz@fda.hhs.gov, 240-402-4654; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 7301, Silver Spring, MD 20993, stephen.ripley@fda.hhs.gov, 240-402-7911.

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I. Executive Summary

Purpose of the Regulatory Action

We are proposing to revise our existing regulations in subpart B of part 300 (21 CFR part 300) on prescription fixed-combination drugs and establish new provisions applicable to prescription and nonprescription fixed-combination and co-packaged drugs and combinations of active ingredients under consideration for inclusion in an OTC monograph. Although current regulations exist for prescription fixed-combination drugs (current § 300.50 (21 CFR 300.50)) and combinations of active ingredients under consideration for inclusion in an OTC monograph (current § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)), they use slightly different language to state the same requirements. In addition, current § 300.50 does not mention co-packaged drugs even

though the Agency's long-standing policy has been to apply the requirements to co-packaged drugs. The proposed revisions would harmonize the requirements for prescription and OTC products and make them consistent with long-standing Agency policy.

Fixed-combination or co-packaged drugs are intended to provide greater effectiveness (either by having a greater effect for a single indication or by treating more than one indication) than either ingredient alone, or by having one active ingredient enhance the safety or effectiveness of another active ingredient. Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and related regulations, FDA has the authority to require specific types of evidence demonstrating that prescription fixed-combination or co-packaged drugs and OTC ingredients used in combination provide enhanced safety or effectiveness and can be labeled as such. This proposed rule describes the requirements applicants must meet to demonstrate that their fixed-combination or co-packaged drugs are safe and effective.

Under section 502(a) of the FD&C Act (21 U.S.C. 352(a)), prescription and OTC drugs are deemed "misbranded" if their labeling is false or misleading "in any particular." Section 201(n) of the FD&C Act (21 U.S.C. 321(n)) states that labeling is misleading if it fails to reveal facts that are material with respect to the consequences which may result not only from the use of the product as labeled but from the use of the product under such conditions of use as are customary or usual. Information on how each ingredient in a combination contributes to the effect of the combination is a fact "material" to the consequences that may result from customary use of that product. Thus, it is within FDA's authority to require such testing as is necessary to establish the safety and effectiveness of ingredients used in combination.

Summary of the Major Provisions of the Regulatory Action

The proposed rule would apply to both prescription and OTC fixed-combination and co-packaged drugs that are subject to approval under a new drug application (NDA) under section 505 of the FD&C Act (21 U.S.C. 355), or a biologics license application (BLA) under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), and to combinations of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330. It does not apply to individual natural-source drugs, which are drugs derived from natural raw materials, even though those drugs may contain multiple ingredients derived from the same source.

Proposed § 300.53 sets forth the requirements for combinations of active ingredients under consideration for inclusion in an OTC monograph and prescription and OTC fixed-combination and co-packaged drugs. Under proposed § 300.53, two or more active ingredients may be combined in a fixed-combination or co-packaged drug or included as a combination in an OTC monograph when two requirements are met.

First, under proposed § 300.53(a)(1), each active ingredient must make a contribution to the effect(s) of the combination, enhance the safety or effectiveness of an active ingredient, or minimize the potential for abuse of an active ingredient. Second, under proposed § 300.53(a)(2), the dosage of each active ingredient (amount, frequency of administration, and duration of use) must be such that the combination is safe and effective and provides rational concurrent therapy.

Under proposed § 300.53(b)(1), applicants and "interested persons" (persons seeking a change in an OTC monograph) who seek approval of a combination must state the intended use of each active ingredient in the combination. This requirement ensures that the therapeutic purpose

of all active ingredients, even those that might not be considered active ingredients in other contexts, is claimed.

Under proposed § 300.53(b)(2), applicants and interested persons must provide sufficient evidence to demonstrate that their products meet the requirements of § 300.53(a), including evidence demonstrating the contribution of each active ingredient to the effect(s) of the combination. The amount and type of data and information needed may vary depending on a number of factors, including the therapeutic intent of the combination.

Because there are some products for which it would be infeasible or medically unreasonable or unethical to meet the requirements of this proposed rule, proposed § 300.60 would give FDA the authority to grant a waiver of some or all of the requirements of the proposed rule at the request of an applicant or interested person or on its own initiative. In addition, FDA may grant a waiver for products that contain a subset of the components contained in a natural-source drug or a product that has already received a waiver under the proposed rule. FDA may grant a waiver of any of the requirements of proposed § 300.53 depending on the evidence submitted.

Costs and Benefits

The Agency has determined that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

II. Background

We are proposing to revise our existing regulations in subpart B of part 300 on prescription fixed-combination drugs and establish new provisions applicable to prescription and nonprescription fixed-combination and co-packaged drugs and combinations of active ingredients under consideration for inclusion in an OTC monograph.

The proposed rule would apply to fixed-combinations (two or more active ingredients are combined at a fixed dosage in a single dosage form) of drugs (Refs. 1 to 5),[1] as well as to co-packaged drugs (two or more separate drugs in their final dosage forms that are intended to be used together for a common or related therapeutic purpose and that are contained in a single package or unit) and combinations of active ingredients not already described in an OTC monograph.[2]

A. Regulatory History

Current FDA regulations contain requirements applicable to fixed-combination drugs. The provisions on "fixed-combination prescription drugs for humans" are set forth in § 300.50. The requirements for fixed-combination drugs that are marketed without a prescription and that are included in the OTC Drug Review are described in § 330.10(a)(4)(iv).

1. Fixed-Combination Drugs

In the Federal Register of February 18, 1971 (36 FR 3126), FDA issued a "proposed statement" on fixed-combination prescription drugs. In this document, we said that the proposed statement on fixed-combination drugs was intended as amplification of the requirement that an NDA or antibiotic drug application for a fixed-combination drug must be supported by substantial evidence that each ingredient designated as active makes a contribution to the total effect that the drug combination is represented to have and purports to possess. The proposed statement was issued as a regulation and it represented the logical application of the statutory and regulatory

[1] For purposes of this proposed rule, we will use the term "drug" to include all products that fall under the definition of "drug" in section 201(g) of the FD&C Act, which includes biological products that meet that definition, but does not include products that meet the definition of "device" under the FD&C Act (21 U.S.C. 301, et seq.). We also consider dietary supplements that are combined into a single dosage form with, or co-packaged with, a drug to meet the definition of "drug" under section 201(g) of the FD&C Act. This proposed rule does not otherwise address nor affect FDA policy on dietary supplements.

[2] For ease of reference, the term "combination" is used throughout this preamble to refer to these types of products collectively.

requirements for demonstrating effectiveness to the special case of fixed-combination drug products. The proposed statement noted experts' agreement that a fixed-combination drug product must have an advantage to the patient over and above that obtained when one of the individual components is used in the usual safe and effective dose. In the Federal Register of October 15, 1971 (36 FR 20037), we adopted a revised statement on these drugs in the form of 21 CFR 3.86, which later became § 300.50 (40 FR 13494, March 27, 1975).

Current § 300.50 explains how the requirements for demonstrating the safety and effectiveness of a drug submitted under section 505(b)(1) or (2) of the FD&C Act and subject to FDA's implementing regulations in part 314 (21 CFR part 314) apply to prescription fixed-combination drugs. Under current § 300.50(a), two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. "Special cases" of this general rule are when a component is added to enhance the safety or effectiveness of the principal active ingredient or to minimize the potential for abuse of the principal active ingredient.

2. Drug Efficacy Study Implementation Review of Fixed-Combination Drugs

Paragraphs (b) and (c) of current § 300.50 relate to Agency determinations about the effectiveness of drugs under the Drug Efficacy Study Implementation (DESI) review, which FDA initiated in response to the Kefauver-Harris Drug Amendments to the FD&C Act (Pub. L. 87-781). The Kefauver-Harris Drug Amendments required FDA to assess the effectiveness of drugs that the Agency had previously approved for safety under the FD&C Act between 1938 and 1962. When the fixed-combination drug regulations in § 300.50 were established in 1971 (36 FR 20037), the

DESI review was ongoing for many DESI drugs. A significant number of the drugs undergoing DESI review were fixed-combination drugs. According to current § 300.50(b), if a fixed-combination drug that is the subject of an NDA approved before 1962 has not been recognized as effective by FDA based on the Agency's evaluation of the appropriate National Academy of Sciences-National Research Council (NAS-NRC) panel report,[3] or if substantial evidence of its effectiveness has not otherwise been presented, changes in formulation, labeling, or dosage may be proposed, and any resulting formulation must meet the criteria in current § 300.50(a). Under current § 300.50(c), a fixed-combination prescription drug for humans is considered to be in compliance with § 300.50 if FDA has determined the drug to be effective based on evaluation of an NAS-NRC report on the fixed-combination drug.

Because most of the few, still-pending DESI proceedings are in advanced stages, we do not believe that it is necessary to maintain provisions in the fixed-combination drug regulations that address the DESI review. Therefore, current § 300.50(b) and (c) are omitted from this proposed regulation. Under this proposed rule, the manufacturer of a DESI drug could still propose a change in formulation, labeling, or dosage to meet the requirements of this proposed rule, and any DESI proceeding that is still pending when the final rule publishes will be subject to the requirements of the final rule.

3. OTC Combination Drugs

In FDA's consideration of OTC combinations under the OTC Drug Review, the Agency has applied a standard similar to § 300.50(a) under § 330.10(a)(4)(iv) in the development of OTC monographs. An OTC drug that combines two or more safe and effective active ingredients may

[3] Under DESI, FDA contracted with NAS-NRC to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. NAS-NRC created panels to review these drug products; the panels' reports were submitted to FDA, which reviewed and reevaluated the finding of each panel and published its findings in Federal Register notices.

be generally recognized as safe and effective (GRASE) when the following criteria are met: (1) Each active ingredient makes a contribution to the claimed effect(s); (2) combining the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and (3) the fixed-combination, when used in accordance with labeling that provides adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. Combinations of active ingredients described in an OTC drug monograph may be marketed without prior Agency approval. Those combinations that are not described in a proposed tentative final monograph (TFM) or OTC monograph must either be added to the applicable OTC monograph or be approved under the NDA or abbreviated new drug application (ANDA) provisions in section 505 of the FD&C Act before they may be marketed in the United States.

4. Requirements for Fixed Combination Drugs and OTC Combination Drugs

Current §§ 300.50 and 330.10(a)(4)(iv) are not identical. Section 330.10(a)(4)(iv) refers to combinations of "active ingredients" rather than "components," the term used in the prescription fixed-combination drug regulations; however, we do not believe this is a substantive difference because we have interpreted "component" in § 300.50 to mean active ingredient. Section 330.10(a)(4)(iv) specifically states that the combining of active ingredients must not decrease the safety or effectiveness of any individual active ingredient, whereas, § 300.50 does not specifically address this point. A prescription fixed-combination drug must be "safe and effective for a significant patient population requiring such concurrent therapy," (§ 300.50(a)), while an OTC combination of active ingredients must provide "rational concurrent therapy for a significant proportion of the target population" (§ 330.10(a)(4)(iv)).

In addition, unlike the prescription fixed-combination drug regulations, the OTC combination standard does not specifically refer to the addition of a component to enhance the safety or effectiveness, or minimize the potential for abuse, of the principal active ingredient. However, FDA's guidance document entitled "General Guidelines for OTC Drug Combination Products" (OTC combination guidance), issued in 1978 (available at http://www.fda.gov/Drugs under "Guidances (Drugs)"), states that an ingredient claimed to be a pharmacological adjuvant (i.e., to enhance or otherwise alter the effect of another active ingredient) will be considered an active ingredient and may be included as part of a combination only if it meets the requirements of § 330.10(a)(4)(iv). Because of the similarities between § 330.10(a)(4)(iv) and proposed § 300.50, we believe that combinations currently described in TFMs (which will have been proposed under the requirements of § 330.10(a)(4)(iv)) will meet the requirements of proposed § 300.50, if this proposed rule is finalized prior to the TFMs.

This proposed rule aims to create uniform requirements for prescription and nonprescription fixed-combination and co-packaged drugs and combinations under consideration for inclusion in an OTC monograph by incorporating the concepts described in the OTC combination guidance, as well as those set forth in current § 330.10(a)(4)(iv) with those described in current § 300.50.

B. Advantages and Disadvantages of Fixed-Combinations and Co-Packaged Drugs

Most approved drugs contain a single active ingredient[4] that has been demonstrated to be safe and effective in treating a particular disease or condition. However, sometimes two or more

[4] As defined in § 210.3.(b)(7) (21 CFR 210.3(b)(7)) and section III.A of this proposed rule, "active ingredient" is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change during the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

active ingredients are combined to provide greater effectiveness (either as a greater effect for a single indication, such as pain, or by treating more than one indication such as pain and insomnia) than either ingredient alone, or to enhance the safety or effectiveness of one of the active ingredients. Although it is almost always possible to take the ingredients separately, the combination might be advantageous in one or more ways. For example, it might be more convenient for patients or might facilitate compliance with a prescribed regimen.

Although fixed-combination drugs can provide convenience, therapeutic benefit, and even economic benefit to patients, they also have potential disadvantages. These include the lack of flexibility in adjusting the dosage of each active ingredient to an individual patient's needs, the related possibility of overexposure, or unnecessary exposure to a particular active ingredient.

Co-packaged drugs raise similar concerns to those associated with fixed-combination drugs, including whether each product contributes to the effect of the combination, whether there is a particular patient population that requires or can benefit from such a combination, and whether the co-packaged drugs can be used together safely and effectively (i.e., the use of the products together does not raise new safety concerns or interfere with the effectiveness of any active ingredient). For example, a drug manufacturer might co-package a lipid-lowering drug with an antihypertensive drug because patients with high cholesterol often also have high blood pressure. In this case, there is an identifiable patient population that needs both drugs. Although there are existing data on the safety and effectiveness of these products individually, before approving their use in combination, FDA would want to be sure that they can be used together safely and that each does not interfere with the effectiveness of the other. It would also be possible for a monograph to allow the marketing of a co-packaged drug in which the individual drugs have been determined to

be generally recognized as safe and effective and also meet the requirements of this proposed rule.[5] Co-packaged day-night cough-cold products might, for example, be included in the monograph for OTC cough-cold drug products in § 341.40 (21 CFR 341.40), and the monograph could specify the appropriate labeling for the co-packaged drug, if needed.

Co-packaged drugs might also pose certain concerns that differ from those of fixed-combination drugs. These include potential confusion regarding labeling and misuse, abuse, or diversion of one of the products. An example of possible misuse is the development of drug-resistant organisms when a patient fails to properly take co-packaged anti-tuberculosis drugs. Labeling confusion could also occur where information on individual product labels is inconsistent with labeling for use of the co-packaged drugs together. Furthermore, there is concern that abuse or diversion of an active ingredient may be easier with a co-packaged drug than with a fixed-combination drug because the desired active ingredient does not need to be chemically separated from the combination. We believe that the requirements in proposed § 300.53 are sufficiently broad to encompass evaluation of these and similar concerns, and it is appropriate to apply the same requirements to co-packaged and fixed-combination drugs.

III. Description of the Proposed Rule

We are proposing to revise our existing regulations on prescription fixed-combination drugs and establish new provisions applicable to prescription and nonprescription fixed-combination and co-packaged drugs approved under a new drug application and to combinations of active ingredients under consideration for inclusion in an OTC monograph, in

[5] An applicant or interested person may seek to modify a final OTC drug monograph to include a co-packaged drug through a citizen petition filed in accordance with 21 CFR 10.30, or, if applicable, through a time and extent application provided for in § 330.14. Co-packaged OTC products not covered by a final monograph (or covered by a TFM pending issuance of a final monograph) or included in the OTC Drug Review would require NDA approval.

subpart B of part 300, as discussed in this document. The following is a description of the proposed regulation.

A. Definitions (Proposed § 300.50)

In revised § 300.50, we propose to define the following terms used in subpart B (entitled "Combination Drugs") of part 300:

1. Active Ingredient

We propose to define "active ingredient" as having the meaning consistent with that used in § 210.3(b)(7), namely: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect (see § 210.3(b)(7)). Whether an ingredient is active or not may depend on its function in the product (e.g., human serum albumin can be a therapeutic product or can be an excipient for a protein therapeutic). The term "component" in this definition is intended to mean "any ingredient," and FDA has consistently interpreted it in this manner in the context of fixed-combination drugs.[6] We note, however, that the term "active ingredient" does not encompass adjuvants incorporated into a vaccine to enhance the antigenic response to the vaccine, since the adjuvant does not furnish independent pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. For combinations that include large molecules (macromolecules), each individual molecular entity would generally be

[6] See 36 FR 3126, Feb. 18, 1971 (this statement is intended as amplification of the requirement that "a new drug … application for a combination drug may be refused unless there is substantial evidence that each component designated as active makes a contribution to the total effect which the drug combination is represented to have and purports to possess").

considered one active ingredient. In other words, a single active ingredient may consist of one macromolecule made up of two or more different chemical entities that are covalently linked. Even if each chemical entity has a distinct activity, such macromolecules would usually be considered a single active ingredient because the covalent bond generally renders the chemical entities inseparable. Naturally derived mixtures are usually considered to contain a single active ingredient because they generally include components whose contribution to the activity of the active ingredient is not known. For the purpose of fixed-combination biological product requirements, a single molecular entity is generally considered one active ingredient.

FDA also has long interpreted the term "other direct effect" in the definition of "active ingredient" to include nutritional effects of dietary supplements. When used as part of a fixed-combination or co-packaged drug, dietary supplements are considered to be an active ingredient in that product and subject to the requirements of this proposed rule. See footnote 1 for additional discussion of the treatment of dietary supplements as drugs when used in combination with a drug.

2. Applicant

We proposed to define "applicant" as any person who, to obtain approval of a fixed-combination or co-packaged drug, submits an NDA under section 505 of the FD&C Act or a BLA under section 351 of the PHS Act.

3. Botanical Raw Material

We propose to define "botanical raw material" as a fresh or physically processed material derived from a single part of a single species of plant,[7] or a fresh or physically processed alga or macroscopic fungus that has not been genetically modified using recombinant DNA technology or

[7] If the plant from which the botanical raw material is derived is microscopic, the entire plant may be used and would be considered one part.

any other process that deliberately changes the genome. Examples of traditional medicines derived from a single part of a single species of plant are isatis leaf (Isatis indigotica Fort.), used in traditional Chinese medicine to treat diseases with high fever and skin eruptions, tanghen root (Codonopsis pilosula (Franch.) Nannf.), used to treat diabetes; and Rauwolfia serpentine for the treatment of hypertension.

We encourage the study and development of botanical substances as botanical drug products. In 2004, we issued guidance for industry, "Botanical Drug Products," on conducting clinical studies of and submitting marketing applications for such products (69 FR 32359, June 9, 2004). The guidance is available on the Internet at http://www.fda.gov/Drugs under "Guidances (Drugs)." Using the principles explained in this guidance, we approved sinecatechin in 2006 and crofelemer in 2012, both of which are botanical new drugs.

4. Co-Packaged Drug

We propose to define "co-packaged drug" as a product that contains two or more separate drugs in their final dosage forms that are intended to be used together for a common or related therapeutic purpose and that are contained in a single package or unit.

Co-packaging two or more drugs might involve, for example, putting these products into the same blister pack, carton, or box, or in separate boxes that are shrink-wrapped together. Some co-packaged drugs have separate labeling for each of the individual products; whereas, other co-packaged drugs have joint labeling. For example, co-packaged Sodium Nitrite Injection and Sodium Thiosulfate Injection (Nithiodote) are marketed for the sequential treatment of acute cyanide poisoning that is judged to be life-threatening. When sodium thiosulfate is sold as a single entity, it is labeled for sequential use with sodium nitrite for treatment of acute cyanide poisoning that is judged to be life-threatening. When sodium thiosulfate is co-packaged with sodium

thiosulfate, it is singly labeled for treatment of acute cyanide poisoning that is judged to be life-threatening. The Monistat 3 Combination Pack for treatment of vaginal yeast infection is an example of a co-packaged OTC product the individual components of which are also sold individually (cool wipes, miconazole nitrate vaginal inserts, and miconazole nitrate cream). Miconazole nitrate vaginal inserts are sold separately as Monistat outside of a combination pack and are labeled for treatment of vaginal yeast infections. Similarly, miconazole nitrate cream is sold individually for treatment of vaginal itching. However, when these products are packaged together in the Monistat 3 Combination Pack, the co-packaged drug has one label for both products.

In recent years, we have reviewed and approved several applications to market co-packaged drugs. Examples include Pravigard PAC (co-packaged pravastatin sodium tablets and buffered aspirin tablets) for reducing the occurrence of serious cardiovascular and cerebrovascular events; co-packaged peginterferon alfa-2a and ribavirin for the treatment of hepatitis C; and co-packaged bismuth subsalicylate (gastrointestinal agent), metronidazole (antiprotozoal and antibacterial agent), and tetracycline hydrochloride (antibiotic) for the treatment of patients with active duodenal ulcer associated with Helicobacter pylori infection. Because our fixed-combination drug regulations in current §§ 300.50 and 330.10(a)(4)(iv) do not specifically address the approval of co-packaged drugs, we have been responding to these applications on a case-by-case basis by applying the statutory standards for safety and effectiveness, as well as applicable regulations for new drugs.

The Agency interprets the act of shrink-wrapping or otherwise packaging two products together, in the absence of any alternative explanation for the packaging such as "convenience" or "value" pack, to be an implied claim that the products are intended to be used together for a

common or related therapeutic purpose. In the case of a dietary supplement co-packaged with a drug, the co-packaging implies that the dietary supplement is intended to be used for a therapeutic purpose, and the dietary supplement will be considered a drug under the FD&C Act (see footnote 1 for additional discussion of the treatment of dietary supplements as drugs when used in combination with a drug).

In the absence of another explanation (such as the "convenience kit" discussed later in this section), packaging two products together makes an implied claim that they are safe and effective when used together. Without proper approval, these products are considered unapproved drugs under section 505(a) of the FD&C Act. Without approved labeling, such products would also be considered misbranded under section 502 of the FD&C Act, including under section 502(n).

In some cases, however, OTC drugs are packaged together for convenience, such as a "travel kit" or "convenience kit" that includes an antiperspirant, an internal analgesic, toothpaste, sunscreen, and/or a sleep aid. In other cases, OTC drugs might be packaged together as two or more shrink-wrapped cartons to be sold as one unit identified as a "special value" or "value pack." These individual drugs are not intended to be used together for a common or related therapeutic purpose. Therefore, these types of kits do not meet the proposed definition of co-packaged drug and would not be subject to the requirements of this proposed rule.

5. Drug

We propose to define "drug" as having the same meaning given this term in section 201(g) of the FD&C Act and including biological products as defined in section 351 of the PHS Act that also meet the definition of "drug" in section 201(g) of the FD&C Act, but not including any product that meets the definition of "device" under the FD&C Act (21 U.S.C. 301, et seq.).

6. Fixed-Combination Drug

We propose to define "fixed-combination drug" to mean a drug in which two or more active ingredients are combined at a fixed dosage in a single dosage form.

We are not proposing to include individual natural-source drugs under the definition of "fixed-combination drug," even when they may contain more than one active component. We do not believe that the current fixed-combination drug regulations were intended to or should apply to a drug that is derived from a single, naturally occurring raw material. Fixed-combination drugs involve deliberate combinations of distinct, single active ingredients, either produced synthetically or isolated and purified from a natural source.

Examples of prescription fixed-combination drugs include the following: ARTHROTEC (diclofenac sodium and misoprostol tablets) for the treatment of osteoarthritis or rheumatoid arthritis in patients at high risk of developing nonsteroidal anti-inflammatory drug (NSAID)-induced gastric or duodenal ulcers; COMBIVIR (lamivudine and zidovudine tablets) for the treatment of HIV infection; and LOTREL (amlodipine besylate and benazepril capsules) for the treatment of hypertension (one of a large number of antihypertensive fixed-combination drugs). Examples of fixed-combination OTC drug products marketed in accordance with OTC drug monographs include, a wide variety of "cough/cold" fixed-combination drugs (containing analgesics-antipyretics, cough suppressants, decongestants, and antihistamines). Fixed-combination OTC drug products marketed under an NDA include Imodium Multi-Symptom Relief (loperamide hydrochloride and simethicone tablets), to relieve diarrhea and gas, and Pepcid Complete (famotidine, calcium carbonate, and magnesium hydroxide chewable tablets), to relieve heartburn.

There are also certain products that, although they are composed of or derived from a single animal, botanical, prokaryotic, fungal, or viral raw material, combine two or more separated

and purified active ingredients and therefore would be regarded as fixed-combination drugs subject to the requirements of proposed § 300.53. These include any products made by inducing and/or copurifying, and then combining, two or more different macromolecules derived from the same raw material where each macromolecule in the fixed-combination drug is necessary to achieve the claimed effect(s).

Our current and long-standing policy is to apply the requirements of current § 300.50 to fixed-combination drugs that are created by combining two or more macromolecules that are separate active ingredients. It should be noted, however, that products such as whole blood, individual or pooled transfusible blood components (e.g., pooled platelets), pooled plasma products, and plasma derivatives from human or animal sources (e.g., immune globulins of general or particular specificity) would not be regarded as fixed-combination drugs, which also would be consistent with our current and long-standing policy.

We also have a current and long-standing policy of applying the requirements of current § 300.50 to products formed by inducing and then purifying two or more macromolecules (proteins or other macromolecules) derived from the same raw material where each induced and purified protein or other macromolecule is necessary to achieve the claimed effect(s) of the product. Inducing macromolecules usually involves treating a source material to elicit the production of two or more macromolecules from a single raw material source. For example, a single animal (raw material source) might be immunized with multiple antigens to induce antibodies of multiple specificities. Another example is combining two treatments that enhance production of different proteins in one cell line, with both sets of proteins contributing to the claimed effect of the product. Even for a product created using a process in which the raw material is not manipulated, if an applicant makes claims about different specific macromolecules

contained in the product, it would be considered a fixed-combination drug and the applicant would be required to demonstrate the contribution of each active ingredient to the claimed effect.

Similarly, a product derived from the purification of an entire set of macromolecules, such as immunoglobulin derived from human plasma, would not be regarded as a fixed-combination drug.

Copurifying macromolecules involves selective purification and extraction of multiple macromolecules away from the rest of the raw material, such as that which occurs during the development of the fibrinogen component of a fibrin/thrombin sealant product. The fibrinogen component can be isolated from plasma in such a way that it contains both fibrinogen and Factor XIII. If the copurified fibrinogen and Factor XIII are isolated and measured to determine whether each improves the performance of the other, and it is determined that they both make a contribution to the fibrin sealant (e.g., hemostatic) activity of the product, such a product would be considered a fixed-combination drug with three active ingredients: Thrombin, fibrinogen, and Factor XIII.

7. Fungal Raw Material

We propose to define "fungal raw material" as a physically processed culture of a single-cell or multicellular organism, including yeasts, molds, and smut.

8. Interested Person

We propose to define "interested person" to mean, with regard to a combination of two or more active ingredients under consideration for inclusion in an OTC monograph, any person who makes a submission under part 330 regarding safety or effectiveness.

9. Natural-Source Drug

We propose to define "natural-source drug" as a drug composed of one single animal, botanical, prokaryotic, fungal, or viral raw material, or derived from one such material using a manufacturing process that involves only physical steps (e.g., solvent extraction, condensation, column purification), and does not involve a chemical reaction (other than esterification, viral inactivation, or prokaryote inactivation) that would modify the covalent bonds of any substance in the original material. This would be true even though the natural-source drug may be considered to contain multiple components that may contribute meaningfully to the drug's pharmacological or therapeutic activity.

The composition of a natural-source drug may be adjusted for assuring quality (e.g., for assuring consistency or purity), but may not be changed in a way that would affect the product's activity (e.g., by selectively increasing or decreasing the concentration of particular components). In this way, we mean to distinguish natural-source drugs from synthetic substances, including synthetic mixtures.

Examples of natural-source drugs include the following:

- Menotropins derived from the urine of postmenopausal women for the induction of ovulation in anovulatory infertile patients.
- Extract from porcine thyroid glands for treating hypothyroidism.
- Extract from porcine pancreas glands for treating pancreatic enzyme deficiency.
- Heparin sodium derived from porcine intestinal mucosa for anticoagulant therapy in prophylaxis and treatment of venous thrombosis.
- Psyllium husk fiber for treatment of constipation.
- Bermuda grass pollen allergenic extract.
- Catechins in green tea extract for treatment of genital warts.

- Polyclonal immunoglobulin to provide protection against infectious diseases.
- Prothrombin complex concentrate products used for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy.

Natural-source drugs differ from the drugs for which current § 300.50 was established in that they do not involve an intentional "combining" of active ingredients. There is no discussion of this type of drug in the regulatory history of § 300.50 or § 330.10(a)(4)(iv), and historically we have not applied the fixed-combination drug requirements to products that contain active ingredients derived from a single, naturally-occurring source. Therefore, we believe that it is appropriate to make clear in the regulations that individual natural-source drugs are not fixed-combination drugs and are not subject to this proposed rule.

In addition, we contemplate that the raw materials contained in natural-source drugs exist in nature or result from a traditional breeding practice or a conventional laboratory gene modification technique such as ultraviolet radiation or non-targeted chemical mutagenesis. Plants or animals that are genetically modified in these ways result from a process that can produce multiple, unpredictable variants of the genome of an organism, similar to the process that occurs in nature. In contrast, genetic modification by a process involving recombinant DNA technology or any other gene modification technology produces a deliberate change to the genome of an organism. Thus, plants, animals, or microorganisms whose genetic structure has been modified by recombinant DNA technology would not be appropriate sources for natural-source drugs because the intent is to produce a particular gene product with well-defined active ingredients. Included among such products are transgenic plants, transgenic animals, and recombinant DNA-derived microorganisms and other cells.

Similarly, we assume that the components of natural-source drugs have not been altered or deliberately mixed in a way that would change the activity or effect of the product. We understand that, for certain products, such as fish-oil mixtures or conjugated estrogens, it is important to adjust the levels of the individual components to maintain uniformity of effect and overall product quality. This kind of adjustment would not be expected to alter the effect or activity of the product and is an acceptable practice for maintaining quality. However, a product that is the result of a deliberate, selective extraction and mixing of components, even if derived from a naturally occurring raw material, does not meet the definition of natural-source drug, but rather would be considered a fixed-combination drug. These products are further described in the discussion of inducing and/or copurifying two or more different macromolecules under the definition of "fixed-combination drug" in section III.A.6.

In addition, drugs made from multiple raw materials (such as a product made from parts of different plants) would not be considered natural-source drugs because they involve an intentional combining of multiple different raw materials, each of which might contain a separate active ingredient, for the purpose of treating a particular disease, condition, or set of symptoms. One example of such a drug is botulinum antitoxin, which is made by immunizing several horses with one of seven distinct botulinum toxins and blending the plasma from the animals to make a single product that is active against seven toxins. Mixed (multiple source) allergenic products are another example of a drug made by intentionally combining more than one raw material. Stallergenes' ORALAIR, a sublingual allergen extract, contains a mixture of freeze-dried extracts from the pollens of five grasses, including Kentucky bluegrass, orchard, perennial rye, sweet vernal, and timothy. These types of products would be subject to this proposed rule, but may be

eligible for a waiver under proposed § 300.60 on the grounds that clinical trials to show that each component contributes to the effect of the combination would be scientifically infeasible.

Finally, it is important to note that, although the requirements of proposed § 300.53 would not be applied to natural-source drugs, to obtain marketing approval of these products, an applicant would still need to provide evidence demonstrating that the natural-source drug meets the requirements for approval under section 505 of the FD&C Act or section 351 of the PHS Act, or is appropriate for inclusion in an OTC monograph.

10. Prokaryotic Raw Material

We propose to define "prokaryotic raw material" as a physically processed culture of bacteria or other cellular organism lacking a true nucleus and nuclear membrane. Prokaryotes are composed of bacteria and blue-green bacteria (formerly referred to as blue-green algae).

11. Rational Concurrent Therapy

We propose to define "rational concurrent therapy" as medically appropriate treatment for a patient population defined in the drug's labeling. That is, the defined patient population can benefit from all of the active ingredients at the specific doses present, given for a similar duration of treatment, and not be adversely affected by receiving them in combination.

When we refer to a "defined patient population" in this definition, we mean that there is an easily identifiable patient population for the combination in question that will be specifically described in the drug's labeling. When we say that the defined patient population will not be adversely affected, we mean, for example, not adversely affected by being exposed to drugs that interact harmfully, being restricted to particular doses of a drug when a wider range of doses is needed for proper administration, and having to take two or more active ingredients as extended treatment when one or more of these ingredients may be needed only for a short period of time.

Rational concurrent therapy does allow for the treatment of more than one indication, as long as there is a defined patient population for which the combination provides medically appropriate treatment.

The requirement that the patient population be identified in the label is currently required under § 300.50, but is not currently in § 330.10. However, identifying the patient population has been the practice in circumstances when an OTC drug is only appropriate for certain patient populations, so we do not believe this proposed requirement will require a change in existing labeling for OTC monograph drugs.

12. Single Animal Raw Material

We propose to define "single animal raw material" as a single organ, human cell, tissue, cellular- and tissue-based product, or bodily fluid collected from any human or nonhuman animal species that has not been genetically modified using recombinant DNA technology or any other process that deliberately changes the genome. In certain cases, multiple parts of an animal may be used in a single animal raw material. For example, a drug that is derived from an invertebrate animal species (including multiple parts or all of an invertebrate animal) may be considered a single animal raw material. The organs and tissues of invertebrate species (e.g., insects) tend to be much smaller than those of most vertebrates. Consequently, with invertebrates, it is much more likely that a combination of more than one organ, tissue, or fluid--or an entire organism--will be used for various therapeutic indications.

13. Viral Raw Material

We propose to define "viral raw material" as a minimally processed culture of a virus. The virus in culture may exist in nature or may have been attenuated or inactivated through selection or by physical and/or chemical means.

14. Waived Product

We propose to define "waived product" to mean: (1) An approved fixed-combination or co-packaged product for which a waiver has been granted under § 300.60 or (2) a combination of active ingredients included in an OTC monograph that has been GRASE for which a waiver has been granted under § 300.60.

B. Applicability of the Proposed Rule (Proposed § 300.51)

Proposed § 300.51 states that subpart B of part 300 (currently containing the provisions on prescription fixed-combination drugs for humans) applies to both prescription and OTC fixed-combination and co-packaged drugs that are subject to approval under an NDA under section 505 of the FD&C Act, or a BLA under section 351 of the PHS Act, and to combinations of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330. It does not apply to individual natural-source drugs.

This proposed rule applies to prescription or OTC fixed-combination or co-packaged drugs that require an NDA or a BLA for marketing approval. In addition, OTC combinations cannot be GRASE under § 330.10 unless they meet the requirements in proposed § 300.53. This means that, consistent with our current regulations, compliance with proposed § 300.53 would be necessary to add a new combination of active ingredients to an OTC monograph in accordance with § 330.10(a)(12). Or, to obtain approval of a combination of two active ingredients that are each contained in a different final monograph, an applicant may submit an NDA deviation under § 330.11, which would also have to comply with proposed § 300.53.

The proposed rule would not apply to combination products[8] involving devices (e.g., drug/medical device or biological product/medical device combinations) and does not alter

[8] As stated in this section of the document, under § 3.2 (21 CFR 3.2), a "combination product" involves a combination,

determination of primary jurisdiction for combination products under part 3 (21 CFR part 3). Part 3, entitled "Product Jurisdiction," governs the determination of what organizational component within FDA will be designated to have primary jurisdiction for premarket review and regulation of combination products (i.e., any combination of a drug and device; a device and a biological product; a biological product and a drug; or a drug, biological product, and a device). A fixed-combination or co-packaged drug may also meet the definition of a "biological product" and be assigned to either the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research for FDA organizational jurisdiction purposes. This does not affect the applicability of this proposed rule.

C. Requirements of the Proposed Rule (Proposed § 300.53)

Proposed § 300.53 sets forth the requirements for combinations of active ingredients under consideration for inclusion in an OTC monograph and prescription and OTC fixed-combination and co-packaged drugs. Under proposed § 300.53, two or more active ingredients may be combined in a fixed-combination or co-packaged drug or included as a combination in an OTC monograph when the proposed requirements are met.

First, under proposed § 300.53(a)(1), each active ingredient must make a contribution to the effect(s) of the combination, enhance the safety or effectiveness of an active ingredient, or minimize the potential for abuse of an active ingredient. Most often, two or more active ingredients are combined in a single dosage form or are co-packaged so that patients or consumers who are taking both active ingredients can more conveniently obtain the therapeutic benefits of each active ingredient. In this case, an applicant or interested person would be required to show

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under specified circumstances, of two or more regulated components in one of the following combinations: Drug/device, biological product/device, drug/biological product, or drug/device/biological product (see § 3.2(e)(1) through (4)).

that each active ingredient contributes to the effect(s) of the combination. In other cases, active ingredients are combined to enhance the safety or effectiveness of one or more of the active ingredients or to minimize the potential for abuse of one of the active ingredients. In these cases, an applicant or interested person would be required to demonstrate that the active ingredients perform as claimed.

Second, under proposed § 300.53(a)(2), the dosage of each active ingredient (amount, frequency of administration, and duration of use) must be such that the combination is safe and effective and provides rational concurrent therapy. We note that, in the context of the OTC monograph, some monographs indicate that dosing for combinations should not "exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph," but remain silent on minimum dosage limits. For a combination under a monograph or proposed to be included in a monograph, to satisfy the requirements of either this proposed rule or current § 330.10(a)(4)(iv), the dosing for the individual active ingredients in the combination must not exceed the maximum dosage limits for the single entities (if these are marketed separately) and must meet the minimum effective dosage established in the monograph. For example, if the monograph specifies that an individual active ingredient is to be dosed every 4 hours, that active ingredient could not be combined with another active ingredient that is to be dosed every 6 to 8 hours because there is no way to write directions for use with a dosing interval that would achieve the minimum effective dose for both ingredients without exceeding the maximum dose for one of them.

We note that, under section 351(d)(1) of the PHS Act, a BLA must demonstrate that the product is "safe, pure, and potent" to be approvable; whereas, section 505(d) of the FD&C Act requires proof of safety and substantial evidence of effectiveness for approval of an NDA.

Nevertheless, we believe that referring to effectiveness in proposed § 300.53(a) is appropriate and consistent with statutory and regulatory provisions regarding biological products. This is because the Agency has long interpreted "potency" to include effectiveness.[9]

Under proposed § 300.53(b)(1), we explain that applicants or interested persons must state the intended use of each active ingredient in the combination. This requirement ensures that the therapeutic purpose of all active ingredients, even those that might not be considered active ingredients in other contexts, is claimed. As noted in footnote 1 and under the definition of "active ingredient" in section III.A.l., FDA considers a dietary supplement to be a drug and considers it to be intended to furnish a therapeutic effect when it is combined with a drug in a prescription or OTC fixed-combination or co-packaged drug or is part of a combination under consideration for inclusion in an OTC monograph.

Under proposed § 300.53(b)(2), we explain that applicants and interested persons must provide sufficient evidence to demonstrate that their products meet the requirements of proposed § 300.53(a), including evidence demonstrating the contribution of each active ingredient to the effect(s) of the combination. The amount and type of data and information needed to demonstrate such a contribution may vary depending on a range of factors, including the types and number of active ingredients, the nature of the therapeutic intent of the product (e.g., a combination of active ingredients intended to treat the same sign or symptom; a combination of active ingredients intended to treat different, but concurrently occurring, signs or symptoms; or a combination in which one ingredient is intended only to potentiate the other ingredient that is active against the disease or condition), and whether the individual active ingredients are already approved as single agents for the same indication(s) as are sought for the fixed-combination or co-packaged drug.

[9] 21 CFR 600.3(s); see also guidance for industry on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," available at http://www.fda.gov/Drugs under "Guidances (Drugs)."

The most common scenario for development of fixed-combination or co-packaged drugs involves combining two or more drugs that are already approved for use as single agents. In these types of fixed-combination or co-packaged drugs, the drugs to be combined may be directed at the same sign or symptom of the same disease or condition, at different signs or symptoms of the same disease or condition, or at different diseases or conditions. Less often, a fixed-combination or co-packaged drug will include one approved drug and an additional active ingredient that is intended to enhance its safety or effectiveness but that has no independent therapeutic effect. For fixed-combination or co-packaged drugs that are made up of already-approved drugs, the individual drugs in the combination are generally well-characterized and development is focused primarily on characterizing the safety and effectiveness of the combination and the contribution of each component. In these cases, the data needed to demonstrate the contribution of each active ingredient to the effect of the combination could include some or all of the following: Controlled clinical trials showing a contribution of each active ingredient to the claimed effect; controlled studies showing an effect of each active ingredient on a pharmacologic parameter or biomarker considered predictive of the therapeutic effect; clinical pharmacology data; in vitro data; and/or animal model data.

FDA is also aware of a growing interest in the development of two or more new investigational drugs (i.e., drugs that have not been previously developed) for use in combination, either as individual agents labeled for use with one another or as a fixed-combination or co-packaged drug. There is particular interest in such development for targeted cancer and anti-infective therapies. In contrast to fixed-combinations or co-packages of previously approved drugs, new investigational products are not well-characterized. Therefore, this type of development is inherently more complex and requires studies to characterize not only the

combination, but also the individual agents to the extent necessary and feasible. Because of the complexity involved in development of two new investigational drugs, FDA has provided guidance to assist sponsors (see guidance for industry on "Codevelopment of Two or More New Investigational Drugs for Use in Combination," available at http://www.fda.gov/Drugs under "Guidances (Drugs)").

Proposed § 300.53(c) states that the statement and evidence specified in proposed § 300.53(b) must be provided in an NDA or a BLA or, if an interested person seeks to include the combination in an OTC monograph, in a submission under part 330. The information showing that a fixed-combination or co-packaged drug meets the requirements of § 300.53 would be included in the data on effectiveness that is needed for the approval of an NDA under § 314.50(d)(5) (21 CFR 314.50(d)(5)), for the approval of a BLA under § 601.2(a) (21 CFR 601.2(a)), or for inclusion of the combination in an OTC monograph under part 330. Regarding NDAs, this would include an NDA requesting approval of an OTC combination that deviates in some respect from a final monograph in accordance with § 330.11. During the development of a fixed-combination or co-packaged drug, we may generally discuss with the sponsor what clinical trial data or other information might be needed to demonstrate that the product meets these requirements.

In the following subsections of this document, we discuss the data and information that might be needed to demonstrate the contribution of each active ingredient to the effect of a combination. As this discussion illustrates, there is considerable flexibility in the amount and types of new or existing data that would be needed, and applicants and interested persons should provide scientific justification for the testing and data that might be needed to discuss the matter with FDA. We also understand that, in some cases, it may be medically unreasonable or unethical

or scientifically infeasible to conduct new clinical studies, and existing data may not be adequate to fulfill the requirements of proposed § 300.53. In these cases, a waiver from the requirement to demonstrate the contribution of each active ingredient to the claimed effect may be an option (see proposed § 300.60).

Finally, it is important to note that it is not always a requirement that a fixed-combination formulation be used in a factorial study. The data from a factorial study in which the individual active ingredients are administered separately can be relied upon to support an application for a fixed-combination drug if the study data is linked to a fixed-combination formulation by a bioavailability study.

1. Combinations in Which the Individual Active Ingredients Are Directed at the Same Sign, Symptom, or Condition

Active ingredients that have different mechanisms of action may be combined to treat the same sign, symptom, or condition if the active ingredients, when used together, can be proven to provide a benefit greater than each of the active ingredients used alone at its therapeutic dose. For such combinations, in which the effect of each active ingredient is directed at the same sign or symptom of a disease or condition, a factorial study is typically used to demonstrate that the combination has a larger treatment effect than one or more of the active ingredients alone. A factorial study for a combination of n active ingredients would ordinarily be designed to show that the n active ingredient combination is more effective than all possible n-1 active ingredient combinations. Thus, for a combination with two active ingredients, a factorial study would have three arms--the combination (AB) and the individual drugs contained within it (A) and (B)--and would be designed to demonstrate that AB has a larger effect than A alone and B alone (AB versus A and AB versus B). For a combination with four active ingredients, a factorial design would

compare the combination (ABCD) to all possible three-drug combinations of the four active ingredients (ABC, ABD, ACD, and BCD).

If a factorial study is needed to demonstrate the contribution of each active ingredient in a combination, and the individual active ingredients are all previously approved and the magnitude and duration of effect of each active ingredient is well characterized, it may be possible to conduct a study of shorter duration than was required for initial approval. It also may be possible to study the effect of the combination on a subset of the endpoints used for approval of the active ingredients, or even a different endpoint such as a pharmacological endpoint, if the active ingredient is well understood.

In certain cases, a new factorial study may not be needed. For example, FDA guidance for industry on the development of combinations of antiretrovirals for the treatment of HIV describes situations in which existing data can be used to demonstrate the contribution of the individual active ingredients, including clinical data on use of the individual ingredients in a combination, in clinical pharmacologic data, and in nonclinical data (Ref. 6). As discussed in that guidance, for a fixed combination of two previously approved drugs in this class, new clinical data would ordinarily be needed only to demonstrate that the bioavailability of the fixed-combination drug is comparable to that of the active ingredients administered individually. The same would be true for a co-packaged drug developed for the treatment of HIV.

The guidance also points out that, in some cases, it may be possible to use data from a previously approved fixed-combination drug to partially support an application for a new fixed-combination drug if the previously approved product is similar to the new product. Similarly, FDA guidance on demonstrating efficacy of fibrin sealant products recommends that overall efficacy of a fixed-combination fibrin sealant drug be demonstrated in clinical trials, but

provides that the contribution of each active ingredient may be demonstrated using nonclinical methods (Ref. 7).

In some cases, it may not be possible to conduct a factorial study because the study would be unethical. For example, it would be unethical to conduct a factorial study with a mortality or heart attack outcome comparing a fixed-combination drug with two active ingredients to its individual active ingredients if both active ingredients have established beneficial effects on mortality or major morbidity endpoints (e.g., an antiplatelet drug and a lipid-lowering drug that each reduce the risk of death, stroke, and heart attack). In that case, subjects randomized to the single-drug groups would be denied therapy that is known to decrease the incidence of major cardiovascular events and death. On the other hand, a short-term study of the platelet-inhibiting and lipid-lowering effects of the combination would be ethical and might support outcome claims, depending on available data or concomitant use of the drugs. Similarly, it may not be possible to compare an antiviral fixed-combination drug to the individual active ingredients if there is known rapid development of resistance to monotherapy. It also may not be needed if the studies of the single entities used together show improved long-term effectiveness.

In the case of combinations for which a factorial design is not possible, different approaches could be used to satisfy the requirement to demonstrate the contribution of each active ingredient to the effect of the combination by identifying an existing population in which the added effect of one of the active ingredients could be established. For example, for a fixed-combination drug containing an older antiplatelet active ingredient and a newer lipid-lowering active ingredient, existing studies of the lipid-lowering active ingredient may have included substantial subsets of subjects who were all receiving the antiplatelet active ingredient and who were randomized to the lipid-lowering active ingredient or placebo. These subsets could potentially be

used to demonstrate the added contribution of the lipid-lowering active ingredient. Or, if there were a newer antiplatelet drug (approved after the lipid-lowering active ingredient), there may be studies in which its effect when added to the lipid-lowering active ingredient had been established. In theory, the data from these studies may be adequate to support a general conclusion that a lipid-lowering active ingredient and an antiplatelet active ingredient can be expected to have independent and additive effects when used in combination.

There are also practical constraints on the use of a factorial design as the number of active ingredients in a combination increases. The greater number of active ingredients in a combination, the greater number of comparisons must be performed to demonstrate that each active ingredient contributes to the effect of the combination. At some point, a factorial study design becomes infeasible. The approximate overall power of a factorial study equals the power of the individual comparisons raised to the $\underline{n}^{th}$ power (exponent) where $\underline{n}$ is the total number of comparisons. So, demonstrating the contribution of each active ingredient of a five-ingredient combination requires five pair-wise comparisons--the full combination (ABCDE) compared to each of the possible combinations of the individual active ingredients (ABCD, ABCE, ABDE, ACDE, and BCDE). If each of the comparisons is powered at 90 percent, there is a 90 percent probability that any given comparison will reject the null (no-difference) hypothesis assuming the alternative hypothesis is true (i.e., there is a difference), but only about a 60 percent probability that all five null hypotheses will be simultaneously rejected (i.e., a 40 percent chance that one of the five comparisons will be an erroneous result). In general, for combinations with multiple active ingredients, each individual comparison in a factorial study should be sufficiently powered so that the overall power is at least 80 percent. However, it may not be feasible to enroll the number of subjects needed to provide sufficient power. If the number of active ingredients in a combination renders a factorial design

infeasible, it may be possible to use data from studies evaluating combinations that contain only some of the active ingredients. It also may be possible to use, other types of clinical and nonclinical data and mechanistic information may be available to demonstrate the contributions of the individual active ingredients to the effect of the combination.

Active ingredients that have the same mechanism of action and are directed at the same sign or symptom of a disease or condition should not ordinarily be combined unless there is some advantage over the individual active ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. Thus, simply using half-doses of two pharmacologically similar drugs would not overcome the disadvantages of putting them in a fixed-combination unless the lower doses of the drugs had some advantages, such as fewer or different adverse events or greater effectiveness.

2. Combinations in Which One Active Ingredient Is Intended to Provide a Direct Effect That Enhances the Safety or Effectiveness of Another Active Ingredient

For combinations in which one active ingredient is intended to: (1) Provide a direct effect that either potentiates or makes another active ingredient more tolerable (e.g., using carbidopa to provide a lower dose of levodopa to minimize side effects), (2) minimize an adverse reaction associated with another active ingredient (e.g., using pyridoxine to minimize the toxicity of isoniazid), or (3) reduce the abuse potential associated with another active ingredient (e.g., using an opioid antagonist to reduce the abuse potential of an oral opioid product following manipulation for purposes of abuse), a clinical trial comparing the combination to the disease-active ingredient alone would usually be necessary to demonstrate the contribution of each active ingredient. The trial would have to establish enhanced safety or effectiveness of the combination versus the

disease-active ingredient alone. This would be true whether or not the disease-active ingredient has already been proven to be effective.

3. Combinations in Which Active Ingredients Are Directed at Different Signs or Symptoms of a Disease or Condition

A factorial study is unlikely to be needed to demonstrate the contribution of each active ingredient in a combination where the active ingredients are directed at different signs or symptoms of a disease or condition. Instead, evidence that demonstrates that the active ingredients are effective individually and do not interfere with one another (e.g., pharmacokinetic data) is likely to be adequate to demonstrate the contribution of each active ingredient in this case. However, if there is a real possibility that an active ingredient could affect the safety or effectiveness of another active ingredient (e.g., an active ingredient intended to treat cough might interfere with the effect of a nasal decongestant), a factorial study or other data would probably be needed to demonstrate that the safety or effectiveness of any of the active ingredients is not diminished by combining them.

Many OTC drug monographs, such as the cold cough, allergy, bronchodilator, and anti-asthmatic drug products monograph (part 341), describe acceptable combinations of active ingredients directed at different symptoms arising from a single condition, such as a cold. One example of this would be a fixed-combination drug containing an antipyretic, an antitussive, and a nasal decongestant directed at fever, cough, and congestion, respectively. Combinations such as this, directed at different signs or symptoms of the same disease or condition, would generally not need a factorial study because each active ingredient would be expected to have its usual, independent effect on a particular symptom, and would not be expected to affect the other symptoms.

4. Combinations in Which the Active Ingredients Are Directed at Different Diseases or Conditions

For combinations in which the active ingredients are directed at different diseases or conditions (e.g., common comorbid diseases), it would also generally be expected that each active ingredient would have its usual and independent effect on the disease or condition. Thus, for these types of combinations, it would usually be possible to rely on data demonstrating that the active ingredients are safe and effective when used independently and that no active ingredient interferes with the effect of another. This requirement can usually be satisfied by pharmacokinetic data.

D. Combining One or More Active Ingredients With a Natural-Source Drug, a Waived Product, or a Combination Already Described in an OTC Monograph (Proposed § 300.55)

Proposed § 300.55(a) states that, when a natural-source drug is combined with any other type of active ingredient, the natural-source drug will be considered a single active ingredient for the purposes of fulfilling the requirements of § 300.53. This section is intended to make clear that, for a combination of a natural-source drug and any other active ingredient, proposed § 300.53 would not be interpreted to apply to the components of the natural-source drug.

Proposed § 300.55(b) states that, when a natural-source drug is combined with one or more additional natural-source drugs, each natural-source drug in the combination will be considered a single active ingredient for the purposes of fulfilling the requirements of § 300.53. This is intended to clarify that, when a natural-source drug is combined with another such product, proposed § 300.53 would not be interpreted to apply to the components in the natural-source drugs.

Proposed § 300.55(c) states that, when a waived product is combined with any other type of active ingredient, the waived product will be considered a single active ingredient for the

purposes of fulfilling the requirements of § 300.53. This is intended to clarify that, when a waived product is combined with any other active ingredient, proposed § 300.53 would not be interpreted to apply to the components of the waived product. Waived products are discussed in section III.E.

It is likely that many of these types of combinations would be eligible for a waiver under § 300.60, as discussed in section III.E.

E. Waiver (Proposed § 300.60)

Proposed § 300.60(a) states that "FDA may, at the request of an applicant or interested person or on its own initiative, grant a waiver of any of the requirements under § 300.53 with regard to a fixed-combination or co-packaged drug that is the subject of a pending application under section 505 of the FD&C Act or section 351 of the PHS Act, or a combination of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330, if it finds one of the following: (1) There is a reasonable rationale for the combination of the individual active ingredients, and compliance with any of the requirements of § 300.53 would be infeasible or medically unreasonable or unethical; or (2) the product contains all or a subset of the known or probable components in the same ratio as a natural-source drug or a waived product, provided the product is intended for the same conditions of use as the natural-source drug or the waived product; there is a reasonable basis to conclude that the product would provide a comparable clinical effect to the natural-source drug or the waived product; and, for products containing large molecules (macromolecules), the ingredients have the same principal molecular structural features and overall mechanism of action."

Applicants or interested persons may be granted a waiver from some or all of the requirements of proposed § 300.53, depending on the evidence submitted.

1. Reasonable Rationale

Proposed § 300.60(a) requires that there be a reasonable rationale for the combination of the individual active ingredients in the proposed combination. This requirement ensures that all of the active ingredients in combinations that receive a waiver are appropriate and not extraneously added to the combination in the hope of receiving a waiver. Applicants might fulfill this requirement by referring to existing knowledge or providing data from in vitro or in vivo studies in animals or humans.

2. Infeasibility

Compliance with the requirements of § 300.53 might be infeasible if a proposed combination has so many active ingredients that a factorial study would become absurd (see discussion of statistical issues with large factorial studies in section III.C), and there is no other alternative method to demonstrate the contribution of each active ingredient to the effect of the combination.

Among the types of products for which we would expect to grant a waiver are products used in traditional medicine that are composed of or derived from multiple raw materials from a single source or from raw materials from multiple sources. These products include the following:

- Traditional botanical products composed of multiple botanical raw materials in fixed ratios. These botanical products may be composed of or derived from multiple parts of the same species of plant or from parts of different plant species;[10]
- traditional medicinal products composed of multiple parts of animals; and

[10] An example of a traditional medicinal product made by combining several parts of a single species of plant is Chinese lobelia herb (whole plant with roots, rhizomes, stems, leaves, and flowers of Lobelia chinensis Lour.), used to treat anasarca and ascites. Some traditional medicines combine multiple plants with different properties. For example, Wuling San, which contains Cortex cinnamomi, Rhizoma atractylodis macrocephalae, Rhizoma alismatis, Poria, and Polyporus umbellatus, has been used to treat oliguria caused by nephritis or renal failure. And, Sishen Wan, which contains Fructus psoraleae, Fructus schisandrae, Semen myristicae, and Fructus evodiae, is used in traditional Chinese medicine to treat colitis.

- traditional medicinal products composed of substances derived from more than one type of natural source (e.g., a botanical raw material and a single animal raw material). These products are sometimes used in combination with certain minerals.
- Cellular and gene therapies.

In most cases, these products have so many active ingredients that studies to demonstrate the contribution of each to the effect of the combination would be infeasible. For example, to show the clinical contribution of each active ingredient of a five-active ingredient mixture of raw materials, the study might require a minimum of six or seven arms: One arm for the five-active ingredient product, an arm for each of the five different four-active ingredient treatments (each omitting one component), and possibly a placebo (see section III.C for a full discussion of clinical trial design to fulfill the requirements of this proposed rule). Such a study would be difficult, if not impossible, to conduct.

Therefore, we generally expect to grant a waiver for these traditional products that have a long history of use as a single medicinal product (i.e., in a single solution, tablet, paste, or other form), and that are prepared according to a standardized, published methodology (e.g., pulverization, decoction, expression, aqueous extraction, ethanolic extraction) such as those described in an official pharmacopeia or compendium or a related publication.

We also expect that we would waive the requirements of this proposed rule for certain allergenic products. Allergen patch tests are diagnostic tests applied to the surface of the skin to determine the specific causes of contact dermatitis. An allergenic patch test kit may contain individual patches in which several chemicals that may elicit allergic contact dermatitis are mixed (e.g., black rubber mix, paraben mix, fragrance mix). These tests are combined in this manner because a positive diagnosis regarding any of the allergens in the mix would result in the same

clinical recommendation. Accordingly, there is a reasonable rationale for the product (i.e., the combination of its individual components), and it would be infeasible to require clinical trials to show that each component contributes to the effect of the combination.

A single synthetic process that can produce a large mixture of random polymers (glatiramer acetate) may also be infeasible to study. These large mixtures of random polymers are analogous to the products discussed previously in that determining the contribution of each active ingredient would be similarly difficult.

3. Medically Unreasonable or Unethical

Compliance with the requirements of proposed § 300.53 might be considered medically unreasonable if, for example, each of the active ingredients of a planned fixed-combination drug where the combination is intended to affect survival is known to have an independent effect on survival (e.g., an antihypertensive and a lipid-lowering drug). In such a case, a factorial study with a survival endpoint (A versus B versus AB) should not be required because the single agent treatment arms would prevent patients from receiving the other known lifesaving therapy. If there are no alternative types of data that could be used to demonstrate the contribution of each active ingredient to the effect of the combination, this type of product could be eligible for a waiver (see related discussion of possible alternative data in section III.C).

Similarly, a combination of active ingredients could be effective for a fatal disease for which there is no available therapy[11] (e.g., a malignancy). Although it may be desirable to require an applicant to demonstrate the contribution of each active ingredient in the combination to the effect of the combination using a factorial study or other design with a single agent treatment arm, such a requirement may be medically unethical. If the combination is known to be effective and

[11] For more discussion on FDA's consideration of "available therapy," please see section III.B of the Guidance for Industry entitled "Expedited Programs for Serious Conditions--Drugs and Biologics", May 2014.

there is no available therapy, it would be unethical to withhold the combination from patients in one arm of the study. If there are no alternative types of data that could be used to demonstrate the contribution of each active ingredient to the effect of the combination, this type of product could be eligible for a waiver (see related discussion of possible alternative data in section III.C).

4. Subsets

We do not believe it necessary, from the standpoint of safety or effectiveness, to impose the requirements of this proposed rule on combinations that have similar active ingredients to approved products for which the fixed-combination drug requirements have not been applied or have been waived. To receive a waiver as a subset under this proposed subsection, an applicant or interested person must demonstrate that the active ingredients contained in the product produce a comparable clinical effect to those contained in the original product. Merely encompassing a subset of the active ingredients contained in an approved product is not sufficient to gain a waiver under this provision. The subset of active ingredients must be sufficiently chemically similar to those contained in the approved product to achieve a comparable clinical effect. The concept of a subset contemplates that the active ingredients will remain in the same ratio, but will be a smaller amount. In other words, no product containing a greater percentage of a particular active ingredient than is present in the approved product would be eligible for a waiver.

We propose to apply this concept to fixed-combination and co-packaged drugs containing proteins or other large molecules (macromolecules). However, unlike for small molecules, proteins and macromolecules can differ in ways that do not change their clinical effect. Therefore, we believe it is more appropriate to require that, for fixed-combination and co-packaged drugs involving a subset of proteins or macromolecules, the active ingredients have the same principal molecular structural features and the same overall mechanism of action as the approved product.

This requirement helps ensure that any structural difference would be minor and that the likelihood would be very low that any minor structural difference in an active ingredient would affect its contribution to the product's claimed effect.

For example, an applicant might seek a waiver for a protein drug product with an active ingredient that differs in a post-translational modification from the active ingredient of the approved product. If there was sufficient evidence that the structural difference would be unlikely to alter the contribution of that active ingredient, a waiver might be appropriate. However, if it were known that the structural difference resulted in reduced effectiveness in related products, this might suggest a difference in the mechanism of action of the active ingredient in the proposed product, which would render the product ineligible for a waiver.

Proposed § 300.60(b) states that, if an applicant wishes to request a waiver, it must submit that request with supporting documentation in an application under section 505 of the FD&C Act or section 351 of the PHS Act. If an interested person wishes to request a waiver, that person must do so as part of a submission under part 330. The request for a waiver should explain why the applicant or interested person believes its product fulfills one or more of the waiver requirements of proposed § 300.60(a). Submissions should include evidence demonstrating the safety and effectiveness of the product (including, where appropriate, dose-response studies) and, if appropriate, assurance that the active ingredients or active moieties in the proposed product have a comparable clinical effect as those in the approved product. For infeasibility waivers, applicants and interested persons should explain why they believe it would be infeasible to comply with the requirements of proposed § 300.53. For example, they should explain why it is impossible to conduct any of the studies that would satisfy the requirements of the proposed rule, or, if

conducting a study would be medically unreasonable or unethical, they should discuss why they believe that is the case.

Proposed § 300.60(c) states that "FDA will provide appropriate written notice when the Agency grants a waiver on its own initiative, or grants or denies a request for a waiver. Fixed-combination and co-packaged drugs and combinations of active ingredients under consideration for inclusion in an OTC monograph for which a waiver is granted must still meet all other applicable requirements under section 505 of the FD&C Act, section 351 of the PHS Act, or § 330.10(a)(4) of this chapter, as appropriate." The decision to grant a waiver under proposed § 300.60(a) of the regulations is solely at the discretion of FDA. FDA may choose to grant a full or partial waiver. For products subject to an NDA or a BLA, we will notify the applicant in writing when we grant a waiver, or grant or deny a request for a waiver. For combinations seeking inclusion in an OTC monograph, because the citizen petition process described in 21 CFR 10.25 governs the addition of combinations to a monograph, we will place our decision to grant a waiver, or grant or deny a request for a waiver, in the docket related to the citizen petition. Products for which a waiver is granted must still be shown to meet the requirements for approval under section 505 of the FD&C Act or section 351 of the PHS Act, as appropriate, including requirements for safety and effectiveness, or the requirements for classification of OTC drugs as GRASE under a monograph.

F. Revision of OTC Combination Provision (Proposed § 330.10(a)(4)(iv))

As described in section III.B, proposed § 300.51 states that the requirements of §300.53 would apply to prescription drugs as well as nonprescription drugs that are subject to approval under an NDA. Proposed § 300.51 further states a combination of active ingredients cannot be

GRASE under § 330.10(a)(4)(iv) unless it meets the requirements in § 300.53 (unless it is being marketed in accordance with an existing monograph that includes that particular combination).

Under the proposed rule, § 330.10(a)(4)(iv) would no longer contain separate provisions for OTC fixed-combination or co-packaged drugs. Instead, to make it easier to understand the regulations that apply to OTC combinations, we are proposing to revise § 330.10(a)(4)(iv) to state that a combination of two or more active ingredients that are individually determined to be safe and effective in accordance with the preceding requirements of part 330 must meet the requirements of subpart B of part 300 of the regulations to be GRASE and included in an OTC monograph. If such combination is granted a waiver under § 300.60 of the regulations, it must still meet all other applicable requirements of this subsection to be GRASE and included in an OTC monograph. Unless otherwise specified in the applicable OTC monograph(s), combinations of active ingredients that are included in an OTC monograph may be used in either fixed-combination or co-packaged drugs.

G. Changes to Regulations on Permissible Combinations of Biological Products (Proposed § 610.17)

Section 610.17 of the biological product regulations contains provisions on permissible combinations of biological products. Section 610.17 states that a separate license is required when a licensed product is combined with another licensed product or with a nonlicensable therapeutic, prophylactic, or diagnostic substance.

Under the proposed rule, biological products would be subject to the regulations in subpart B of part 300. To help make this clear to companies that have drug products subject to approval under section 351 of the PHS Act regulations, we propose to revise § 610.17 to state that a drug

product subject to approval under section 351 of the PHS Act may not be combined with another drug except in accordance with subpart B of part 300.

IV. Legal Authority

This rule, if finalized, would amend subpart B of part 300 in a manner consistent with the Agency's current understanding and application of that provision. FDA's legal authority to modify subpart B of part 300 arises from the same authority under which FDA initially issued the regulation (21 U.S.C. 331, 351, 352, 355, 361, 371) and section 330.1 (21 U.S.C. 321, 351, 352, 353, 355, 371) and also, with respect to biological products, section 351 of the PHS Act. Biological products are subject both to section 351 of the PHS Act and to the provisions of the FD&C Act and implementing regulations applicable to drugs, except that manufacturers of biological products covered by approved BLAs are not required to submit NDAs under section 505 of the FD&C Act. References to "drugs" in this section include biological products that are also drugs.

Fixed-combination or co-packaged drugs generally purport to provide greater effectiveness (either in cumulative effect, by treating more than one indication, or by facilitating compliance) than either ingredient alone, or to enhance the safety or effectiveness of one of the active ingredients. Under the FD&C Act and related regulations, FDA has the authority to require specific types of evidence demonstrating that fixed-combination or co-packaged drugs and OTC monograph ingredients used in combination provide enhanced safety or effectiveness and can be labeled as such. This is because the use of any added active ingredient involves some risk, and that risk can only be justified by an added benefit in either safety or effectiveness. This proposed rule describes the requirements applicants must meet to demonstrate that their fixed-combination or co-packaged drugs are safe and effective.

Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's rulemaking authority under section 701(a) has been broadly interpreted.

Under section 502(a) of the FD&C Act, prescription and OTC drugs are deemed "misbranded" if their labeling is false or misleading "in any particular." Section 201(n) of the FD&C Act states that labeling is misleading if it fails to reveal facts that are material with respect to the consequences that may result not only from the use of the product as labeled but from the use of the product under such conditions of use as are customary or usual. With regard to OTC drugs under a monograph, § 330.1 explains that OTC drugs are GRASE and not misbranded if they meet "each of the conditions contained in this part and each of the conditions contained in any applicable monograph." The standards for safety, effectiveness, and labeling are explained in § 330.10(a)(4). Proof of safety may consist of "adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use." Proof of effectiveness must consist of "controlled clinical investigations" demonstrating that the drug "will provide clinically significant relief of the type claimed." Information on how each ingredient in a combination contributes to the effect of the combination is a fact "material" to the consequences that may result from customary use of that product. Thus, it is within FDA's authority to require such testing as is necessary to establish the safety and effectiveness of ingredients used in combinations.

With regard to prescription drugs or nonprescription drugs requiring approval under an NDA, section 505(c) and (d) of the FD&C Act directs FDA to refuse approval if there is a lack of substantial evidence that the drug will have the effect that it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

thereof. The term "substantial evidence" is defined in section 505(d) of the FD&C Act as evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. A drug product is not approvable if there is not "substantial evidence" effectiveness or sufficient evidence of safety. Thus, for fixed-combination and co-packaged drugs, FDA may require such testing as is necessary to establish that the drug is safe and effective for use under the conditions described in the labeling.

Under §§ 314.90 and 314.126(c), FDA has the authority to grant a waiver of any of the requirements for submitting an NDA or any criteria of an adequate and well-controlled study if it finds the applicant's compliance with a requirement is unnecessary or cannot be achieved, the applicant makes an alternative submission that satisfies the requirement, or the applicant otherwise justifies a waiver. Similarly, FDA may waive some or all of the requirements of this proposed rule if an applicant meets certain criteria. Waiver provisions are intended to give applicants flexibility to seek alternative ways of complying with the statutory standards for drug approval. Any drugs that receive a waiver under these provisions are still required to demonstrate safety and effectiveness to meet the statutory requirements for approval.

Section 351 of the PHS Act provides legal authority for the Agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that the products meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (section 351(d) of the PHS Act). The

"potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS Act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

V. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed requirements will have minimal economic impact on small entities (the unit cost of a request for a waiver as a percentage of the average of value of sales for a typical firm would be small--less than 0.15 percent of average sales for firms with 10 to 49 workers and even smaller for other small-size firms), the Agency anticipates that the proposed rule will not have a significant economic impact on a substantial number of small entities and seeks comments on its Initial Regulatory Flexibility Analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before

proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary of Benefits and Costs of the Proposed Rule

The proposed rule would harmonize the requirements for prescription and OTC fixed-combination and co-packaged drugs and clarify the types of studies needed for approval of these products. Although we are unable to quantify or monetize all of the benefits, harmonizing and clarifying current policy would result in benefits to industry because there would be less uncertainty surrounding the requirements for approval of the affected products. This may in turn incentivize the development of new products. We estimated benefits associated with reduction in preparation and review time of information that would not be necessary if the proposed rule were in effect. Estimated annual benefits range between $651,891 and $977,836.

Because the proposed requirements would codify current policy regarding the review of the affected products, there are no costs associated with these proposed requirements. However, the proposed rule would also create a provision under which sponsors can apply for a waiver when certain conditions are met. This proposed provision is a new requirement and would result in costs. Estimated annual costs of preparation and review of the proposed waiver range between $101,858 and $152,787.

The estimated annual benefits and costs are summarized in table 1.

The full discussion of economic impacts is available (Ref. 8) in docket FDA-2011-N-0830

and at

http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of Proposed Rule

Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized (millions $/year)	$0.815	$0.652	$0.978	2012	7%	2014-33	
	$0.815	$0.652	$0.978	2012	3%	2014-33	
Annualized Quantified					7%	2014-33	
					3%	2014-33	
Qualitative	Additional benefits may arise for sponsors who may incur development costs that could be prevented by clarifying the requirements of the products covered by the proposed rule.						
Costs							
Annualized Monetized (millions $/year)	$0.127	$0.102	$0.153	2012	7%	2014-33	
	$0.127	$0.102	$0.153	2012	3%	2014-33	Based on 10-15 waivers per year.
Annualized Quantified	None estimated.						
Qualitative	None estimated.						
Transfers							
Federal Annualized Monetized (millions $/year)	None estimated						
Other Annualized Monetized (millions $/year)	None estimated.						
Effects							
State, Local, or Tribal Gov't	None						
Small Business	Based on the analysis, small business entities covered by the proposed rule could incur costs of $6,701 per waiver or up to 0.15 percent of average annual sales for entities with 10-49 employees and even smaller for all other firms.						
Wages	No estimated effect.						
Growth	No estimated effect.						

VI. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) (PRA). The title,

description, and respondent description of the information collection are given under this section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

We invite comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Regulations on Fixed-Combination and Co-Packaged Drugs and Combinations of Active Ingredients Under Consideration for Inclusion in An Over-the-Counter (OTC) Monograph

Description: The proposed rule would revise existing regulations in subpart B of part 300 on fixed-combination drugs and establish new provisions applicable to fixed-combination and co-packaged drugs and combinations of OTC active ingredients under consideration for inclusion in an OTC monograph. Although current § 300.50 regulates prescription fixed-combination drugs and current § 330.10(a)(4)(iv) regulates combinations of active ingredients under consideration for inclusion in an OTC monograph, they use slightly different language to achieve the same effect. In addition, current § 300.50 does not mention co-packaged drugs even though the Agency's long-standing policy has been to apply the requirements to co-packaged drugs. The proposed revisions would specify the kinds of studies that are needed to meet the requirements of this

proposed rule, and would harmonize the requirements for prescription and OTC products and make them consistent with long-standing Agency policy.

Under proposed § 300.53(a), combinations of active ingredients under consideration for inclusion in an OTC monograph and fixed-combination and co-packaged drugs must meet the following requirements: (1) Each active ingredient makes a contribution to the effect(s) of the combination, enhances the safety or effectiveness of an active ingredient, or minimizes the potential for abuse of an active ingredient and (2) the dosage of each active ingredient (amount, frequency of administration, and duration of use) is such that the combination is safe and effective and provides rational concurrent therapy.

Under proposed § 300.53(b), applicants and interested persons must: (1) State the intended use of each active ingredient in the combination and (2) submit sufficient evidence to meet the requirements in § 300.53(a), including evidence demonstrating the contribution of each active ingredient to the effect(s) of the combination. The amount and types of data and information needed may vary and may include some or all of the following: Data from adequate and well-controlled clinical trials, clinical pharmacology data, in vitro and animal model data, a basis for concluding there is a plausible pharmacologic rationale for the combination, and other relevant information.

Under proposed § 300.53(c), the statement and evidence specified in § 300.53(b) must be included in an NDA (§ 314.50), a BLA (§ 601.2), or a submission under part 330 (§ 330.10) to support inclusion of a combination in an OTC monograph.

FDA already has OMB approval for the submission of data or information under §§ 314.50 and 601.2 (OMB control numbers 0910-0001 and 0910-0338). The proposed regulations clarify

current requirements and FDA policy and, therefore, the proposed changes would not result in the submission of additional data or information.

In addition, the submission of data or information relating to § 330.10(a)(4)(iv) for OTC monographs that have not yet been finalized would be submissions in response to a proposed rule, in the form of comments, which are excluded from the definition of "information" under 5 CFR 1320.3(h)(4) of OMB regulations on the PRA (i.e., "facts or opinions submitted in response to general solicitations of comments from the public, published in the Federal Register or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency's full consideration of the comment").

Under proposed § 300.60(a), FDA may, at the request of an applicant or interested person or on its own initiative, grant a waiver of any of the requirements under proposed § 300.53 with regard to a fixed-combination or co-packaged drug that is the subject of a pending NDA or BLA, or a combination of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330. To grant a waiver, one of the following must exist: (1) There is a reasonable rationale for the combination of the individual active ingredients in the product, and compliance with any of the requirements of § 300.53 would be infeasible or medically unreasonable or unethical; or (2) the product contains all or a subset of the known or probable components in the same ratio as a natural-source drug or a waived product, provided the product is intended for the same conditions of use as the natural-source drug or the waived product; there is a reasonable basis to conclude that the product would provide a comparable clinical effect to the natural-source drug or the waived product; and, for products containing large molecules (macromolecules), the active ingredients have the same principal molecular structural features and

overall mechanism of action as the active ingredients in the natural-source drug or the waived product.

Under proposed § 300.60(b), an applicant must submit a waiver request with supporting documentation in an NDA or BLA, and an interested person must submit a waiver request as part of a submission under part 330.

Existing regulations permit applicants to request waivers of any of the requirements under §§ 314.50 through 314.81for NDAs, and for BLAs, and the information collections associated with such waiver requests generally are approved under existing control numbers. (See § 314.90(a), waiver requests for drugs subject to NDAs and ANDAs (approved under OMB control number 0910-0001); and § 600.90(a), waiver requests for products subject to BLAs (approved under OMB control number 0910-0308)).

Concerning waiver requests submitted for a combination of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330, interested persons would submit such requests as a citizen petition in accordance with § 10.30. FDA currently has OMB approval for the collection of information entitled "General Administrative Procedures: Citizen Petitions; Petition for Reconsideration or Stay of Action; Advisory Opinions" (OMB control number 0910-0183).

Based on information provided in Section V of this preamble and in the Preliminary Regulatory Impact Analysis referenced in Section V, we estimate that FDA will receive approximately 15 waiver requests annually, and that each request will take approximately 50 hours to prepare and submit. The industry burden under the PRA for submitting waiver requests is calculated in Table 2:

Table 2 --Estimated Annual Reporting Burden

	No. of Respondents	No of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Waiver Requests under 21 CFR 300.60(b)	15	1	15	50 hours	750

There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with the PRA (44 U.S.C. 3507(d)), we have submitted the information collection requirements of this proposed rule to OMB for review. Interested persons are requested to send comments on this information collection by (see DATES) to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oira_submission@ombeop.gov.

VII. Environmental Impact

We have determined that under 21 CFR 25.30(h), this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. Proposed Effective Date

We propose that any final rule that may issue based on this proposal become effective 30 days after the date of its publication in the Federal Register. Because we believe this proposed rule clarifies and codifies existing policy, we are proposing that this rulemaking, once finalized, would apply to all pending applications and citizen petitions.

X. Request for Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

XI. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at http://www.regulations.gov.

1. Letter to G. Balkema, President, Bayer HealthCare, L.L.C., from D. Autor, Director, Office of Compliance, Center for Drug Evaluation and Research (CDER), re "Bayer Aspirin With Heart Advantage" (October 27, 2008), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048456.htm.

2. Letter to G. Balkema, President, Bayer HealthCare, L.L.C., from D. Autor, Director, Office of Compliance, CDER, re "Bayer Women's Low Dose Aspirin + Calcium" (October 27, 2008), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048083.htm.

3. Letter to R. McDonald, President and CEO, Procter & Gamble, from D. Autor, Director,

Office of Compliance, CDER, re "VICKS DayQuil Plus Vitamin C" and "VICKS NyQuil Plus Vitamin C" (October 29, 2009), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm188361.htm.

4. Letter to J. Ascher, President and CEO, B.F. Ascher & Co., Inc., from D. Horowitz, Acting Director, Office of Compliance, CDER, re "Melagesic PM Caplets" (October 16, 2001), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM166379.pdf.

5. Letter to K. Irwin, President and CEO, Omni Neutraceuticals, Inc., from D. Horowitz, Acting Director, Office of Compliance, CDER, re "Inholtra Joint Pain Caplets and Inholtra Joint Pain Plus" (October 16, 2001).

6. "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV," available at http://www.fda.gov/Drugs under "Guidances (Drugs)," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166378.pdf.

7. "Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use," available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

8. Food and Drug Administration, Full Disclosure of Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis

on Regulations on Fixed-Combination and Co-packaged Drugs and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter (OTC) Monograph Proposed Rule.

List of Subjects

21 CFR Part 300

Drugs, Prescription drugs.

21 CFR Part 330

Over-the-counter drugs.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR parts 300, 330, and 610 as follows:

PART 300--GENERAL

1. The authority citation for 21 CFR part 300 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 360b, 361, 371; 42 U.S.C. 262.

2. Revise subpart B to read as follows:

Subpart B--Fixed-Combination and Co-packaged Drugs and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter (OTC) Monograph

Sec.
300.50 Definitions.
300.51 Applicability.
300.53 Requirements.
300.55 Combining one or more active ingredients with a natural-source drug, a waived product, or a combination already included in an OTC monograph.
300.60 Waiver.

§ 300.50 Definitions.

As used in this part:

Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Applicant means any person who, to obtain approval of a fixed-combination or co-packaged drug, submits a new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act or a biologics license application under section 351 of the Public Health Service Act.

Botanical raw material means a fresh or physically processed material derived from a single part of a single species of plant, or a fresh or physically processed alga or macroscopic fungus that has not been genetically modified using recombinant DNA technology or any other process that deliberately changes the genome.

Co-packaged drug is a product that contains two or more separate drugs in their final dosage forms that are intended to be used together for a common or related therapeutic purpose and that are contained in a single package or unit.

Drug has the same meaning given this term in section 201(g) of the Federal Food, Drug, and Cosmetic Act and includes biological products as defined in section 351 of the Public Health Service Act that also meet the definition of "drug" in section 201(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(g)), but does not include any product that meets the definition of

device under section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Fixed-combination drug means a drug in which two or more active ingredients are combined at a fixed dosage in a single dosage form. Natural-source drugs are not included under the definition of "fixed-combination drug" unless those drugs are used as ingredients in combination with other ingredients in a single dosage form.

Fungal raw material means a physically processed culture of a single-cell or multicellular organism, including yeasts, molds, and smut.

Interested person means, with regard to a combination of two or more active ingredients under consideration for inclusion in an OTC monograph, any person who makes a submission under part 330 of this chapter regarding safety or effectiveness.

Natural-source drug means a drug composed of one single animal, botanical, prokaryotic, fungal, or viral raw material, or derived from one such material using a manufacturing process that involves only physical steps (e.g., solvent extraction, condensation, column purification) and does not involve a chemical reaction (other than esterification or viral or bacterial inactivation) that would modify the covalent bonds of any substance in the original material. The composition of a natural-source drug may be adjusted for the purpose of assuring quality, but may not be changed in a way that would affect the product's activity (e.g., by selectively increasing or decreasing the concentration of particular active ingredients (for drugs that are biological products) or active moieties (for drugs that are not biological products)).

Prokaryotic raw material means a physically processed culture of bacteria or other cellular organism lacking a true nucleus and nuclear membrane.

Rational concurrent therapy means medically appropriate treatment for a patient population that is defined in the drug's labeling. That is, the defined patient population can benefit

from all of the active ingredients at the specific doses present, given for a similar duration of treatment, and not be adversely affected by receiving them in combination.

Single animal raw material means a single organ, human cell, tissue, and cellular- and tissue-based product, or bodily fluid collected from any human or nonhuman animal species that has not been genetically modified using recombinant DNA technology or any other process that deliberately changes the genome. A drug that is derived from an invertebrate animal species (including multiple parts or all of an invertebrate animal) may be considered a single animal raw material.

Viral raw material means a minimally processed culture of a virus. The virus in culture may exist in nature or may have been attenuated or inactivated through selection or by physical and/or chemical means or recombinant technologies.

Waived product means an approved product or a combination of active ingredients that has been generally recognized as safe and effective and included in an OTC monograph for which a waiver has been granted under § 300.60.

§ 300.51 Applicability.

This subpart applies to both prescription and OTC fixed-combination and co-packaged drugs that are subject to approval under a new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act, or a biologics license application under section 351 of the Public Health Service Act, and to combinations of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330 of this chapter. It does not apply to natural-source drugs unless those drugs are used as ingredients in combination with other ingredients in a single dosage form.

§ 300.53 Requirements.

(a) Combinations of active ingredients under consideration for inclusion in an OTC monograph and fixed-combination and co-packaged drugs (collectively referred to in this section as "the combination") must meet the following requirements:

(1) Each active ingredient makes a contribution to the effect(s) of the combination, enhances the safety or effectiveness of an active ingredient, or minimizes the potential for abuse of an active ingredient; and

(2) The dosage of each active ingredient (amount, frequency of administration, and duration of use) is such that the combination is safe and effective and provides rational concurrent therapy.

(b) Applicants and interested persons must:

(1) State the intended use of each active ingredient in the combination; and

(2) Submit sufficient evidence to demonstrate that the combination meets the requirements in paragraph (a) of this section, including evidence demonstrating the contribution of each active ingredient to the effect(s) of the combination. The amount and types of data and information needed to demonstrate such a contribution may vary and may include some or all of the following: Data from adequate and well-controlled clinical trials, clinical pharmacology data, in vitro and animal model data, a basis for concluding there is a plausible pharmacologic rationale for the combination, and other relevant information.

(c) The statement and evidence specified in paragraph (b) of this section must be included in a new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act, a biologics license application under section 351 of the Public Health Service Act, or a submission under part 330 of this chapter to support inclusion of a combination in an OTC monograph.

§ 300.55 Combining one or more active ingredients with a natural-source drug product or a waived product.

For combinations not already described in an OTC monograph or for proposed fixed-combination and co-packaged drugs:

(a) When a natural-source drug is combined with any other active ingredient, the natural-source drug will be considered a single active ingredient for the purposes of fulfilling the requirements of § 300.53.

(b) When a natural-source drug is combined with one or more additional natural-source drugs, each natural-source drug in the combination will be considered a single active ingredient for the purposes of fulfilling the requirements of § 300.53.

(c) When a waived product is combined with any other active ingredient, the waived product will be considered a single active ingredient for the purposes of fulfilling the requirements of § 300.53.

§ 300.60 Waiver.

(a) FDA may, at the request of an applicant or interested person or on its own initiative, grant a waiver of any of the requirements under § 300.53 with regard to a fixed-combination or co-packaged drug that is the subject of a pending application under section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, or a combination of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330 of this chapter, if it finds one of the following:

(1)(i) There is a reasonable rationale for the combination of the individual active ingredients; and

(ii) Compliance with any of the requirements of § 300.53 would be infeasible or medically unreasonable or unethical; or

(2) The product contains all or a subset of the known components in the same ratio as a natural-source drug or a waived product provided the product is intended for the same conditions of use as the natural-source drug or the waived product; there is a reasonable basis to conclude that the product would provide a comparable clinical effect to the natural-source drug or the waived product; and, for products containing large molecules (macromolecules), the macromolecules have the same principal molecular structural features and overall mechanism of action as those in the natural-source drug or the waived product.

(b) If an applicant wishes to request a waiver, it must submit the waiver request with supporting documentation in an application under section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act. If an interested person wishes to request a waiver, the waiver request must be submitted as part of a submission under part 330 of this chapter.

(c) FDA will provide appropriate written notice when the Agency grants a waiver on its own initiative, or grants or denies a request for a waiver. Fixed-combination and co-packaged drugs and combinations of active ingredients under consideration for inclusion in an OTC monograph for which a waiver is granted must still meet all other applicable requirements under section 505 of the Federal Food, Drug, and Cosmetic Act, section 351 of the Public Health Service Act, or § 330.10(a)(4) of this chapter, as appropriate.

PART 330--OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

3. The authority citation for 21 CFR part 330 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

4. Amend § 330.10 by revising paragraph (a)(4)(iv) to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

* * * * *

(a) * * *

(4) * * *

(iv) A combination of two or more active ingredients that are individually classified as drugs generally recognized as safe and effective in accordance with the requirements of § 300.53 of this chapter must meet the requirements of subpart B of part 300 of this chapter to be generally recognized as safe and effective and included in an OTC monograph. If such combination is granted a waiver under § 300.60 of this chapter, it must still meet all other applicable requirements of this subparagraph to be generally recognized as safe and effective and included in an OTC monograph. Unless otherwise specified in the applicable OTC monograph(s), combinations of active ingredients that are included in an OTC monograph may be used in either fixed-combination or co-packaged drugs.

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PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS

5. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

6. Amend § 610.17 by revising the section heading, designating the existing paragraph as

paragraph (a), and by adding paragraph (b) to read as follows:

§ 610.17 Permissible fixed-combinations.

(a) * * *

(b) A drug product subject to approval under section 351 of the Public Health Service Act may not be combined with another drug product except in accordance with subpart B of part 300 of this chapter.

Dated: December 17, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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